Remarks

Applicants have read and considered the Office Action dated June 27, 2003 and the references cited therein. Reexamination and reconsideration is hereby requested.

The Abstract was objected to because the words "aganst" and "immuno-suppressinve" were misspelled. The Abstract has been amended to correct the errors.

New independent claim 13 now recites that:

1) the diseases or ailments that are to be treated are identified as being "an adverse immune response, inflammation or septic shock"; and

2) the administration of the proteasome inhibitor is specified to occur "16 hours or more after activation of T cells".

This amendment constitutes an effective combination of former claims 1 and 2 and the addition of detail not previously there ("16 hours or more after activation of T cells").

Former claims 6-9 have been cancelled.

Support for the new claims may be found, in particular, at pp. 32-33, 46 and 53-56 of the specification, other portions throughout the application, and in the related figures.

Claims 1-2 were rejected under 35 U.S.C. § 112, first paragraph. New claim 13 is believed to overcome the difficulties previously identified with claim 1. It is submitted that the objection, which states that the specification "does not reasonably provide enablement for a method of reversing the ongoing activity of any activated blood cells ..." is no longer applicable, especially in light of Example 5 of the specification. In addition, the "activity" or more accurately "activities" which are meant to be treated are now clearly identified ("adverse immune response, inflammation or septic shock").

Additionally, Applicants submit that a person of skill in the art would be readily able to recognize when T cells are activated in inflammation, autoimmune diseases and septic shock (all

these pathological conditions involve T cell activation), because activated T cells bear characteristic cell surface markers such as CD25 (Cancer Res. 1985 45:1314-1319; J. Immunol. 1985 134:920-925), CD69 (J. Immunology. 1989, 142:1854-1860), and CD45RO (J Immunol. 1988 Nov 15;141:3249-57). The kinetics of their expression clearly shows whether they have been recently activated. The high expression of some of these markers in patient peripheral blood T cells is an indication of recent T cell activation, and consequently an indication of proteasome inhibitor administration. Applicants assert that the specification is enabling for the pending claims and the rejection is overcome.

Claims 1-2 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The arguments submitted in respect of the objections under 35 U.S.C. § 112, first paragraph should apply here as well. Support for the quantities of proteasome inhibitors in the currently pending claims may be found in Example 5 of the specification and can otherwise be determined in accordance with the teachings in the art. It is now clear that the diseases or ailments that are being targeted are generally "adverse immune response, inflammation or septic shock" and specifically "autoimmune disease or graft rejection".

Former claims 7-9 have been eliminated. Former claim 10, which has been reprised in new claims 15 and 21, clearly indicates that the analogs are of lactacystin or DPBA. Applicants assert that the pending claims overcome the indefiniteness rejections.

Claims 1, 4 and 6-11 were rejected under 35 U.S.C. § 102 as being anticipated by Wang. Applicants assert that the present application has priority over the subject matter that is described in Wang. Applicants' application is based on Canadian Patent Application No. 2,219,867 which was filed on October 31, 1997. The priority date that is established by this application predates the Wang *et al.* reference, which is dated January 15, 1998. Consequently, the Wang et al. reference is not properly citable under 35 U.S.C. § 102 (a) and the rejection should be withdrawn.

Applicants advise the Examiner that there are no changes to the inventorship as a result of the present claim amendments.

The Examiner has rejected former claims 1-12 under 35 U.S.C. § 103 (a) as being unpatentable over Wang *et al.*, Schreiber *et al.*, Armistead *et al.*, and Adams *et al.* Applicants submit that these references do not render obvious the invention that is described in the application under consideration, for the reasons detailed below.

As the Examiner has stated, Wang *et al.* does not expressly teach treatment of individuals with adverse immune response/inflammation/septic shock. In addition, as stated above, the Wang *et al.* reference may not be cited against the present application since the publication date of this reference is subsequent to the priority date of the invention that is the subject of this application.

While the Schreiber international application may appear to be relevant, there are important differences between the invention in Schreiber and that which is recited in the present application. In International Application No. 96/32105 published on October 17, 1996, Schreiber *et al.* teach the use of lactacystin and related analogs to treat inflammation, cancer, autoimmune diseases and graft rejection. In their patent application, they described the synthesis of lactacystin and related analogs which inhibit proteasome activity. Based on the relevant prior art, activation of NF-kB is dependent on the degradation of IkBα and Ikβ. It is this degradation that allows NF-kB to be dissociated from the IKBα and IkBβ. The released NK-kB is thus free to bind to and activate its target genes. Since the degradation is proteasome-dependent, Schreiber *et al.* concluded that activation of NF-kB is proteasome-dependent. Since NF-kB is important in cell activation and death (information that was available in the prior art), they further extrapolated and claimed that lactacystin and its analogs may be used to treat cancer, inflammation, autoimmune diseases and graft rejection.

It should be noted, however, that the activation of NF-kB is a relatively *early* event, occurring within 6 hours of the onset or beginning of an immune response in an episode of inflammation, graft rejection and other forms of adverse immune responses underlying various autoimmune diseases. After this time, the NF-kB pathway is spent and is therefore no longer relevant to the immune response.

It is submitted that novelty of the present invention at least lies in the delayed application of proteasome inhibitors. By way of example, Figures 6C and 6D show the effects of proteasome inhibitors administered 16-48 hours after T cell activation. As described in the application, such delayed administration resulted in an effective and, in fact, a better effect on T cell suppression. The mechanism of such delayed suppression is different from inhibition of the NF-kB pathway which, it is submitted, is the foundation of Schreiber *et al.*'s application. The status of T cells that have already been activated can be determined by surface activation marker expression, such as CD25, CD69, and CD45RO in peripheral blood T cells by flow cytometer according to the prior art. Applicants therefore assert that proteasome inhibitors can be used as medicaments to suppress *already activated* lymphocytes in adverse immune responses, such as ongoing graft rejection, or an episode of autoimmune disease and inflammation flare, at least 16 hours following the start of such an adverse immune response. At that time, the IkBα and IkBβ (and hence, the NF-kB pathway) are no longer in operation.

The Armistead *et al.* patent relates to novel immunosuppressive compounds. Despite the passages highlighted by the Examiner, this patent does not teach or suggest the use of a proteasome inhibitor to treat an adverse immune response, inflammation or septic shock in the manner that is described in the application under consideration, nor does this reference teach the administration of a *combination* of proteasome inhibitor and an immunosuppressant. There are no results in the Armistead patent to even suggest the invention that is described in the present application. Applicants therefore submit that the Armistead patent does not, when considered in combination with the other references cited, render the invention that is described in the present application obvious.

The Adams *et al.* patent discloses novel boronic ester and acid compounds. While such compounds were identified to be suitable proteasome inhibitors (at Column 3), the focus is clearly on *early* events in the immune response. It is notable and significant here that the NF-kB pathway is specifically discussed more than once in the recited passage. For the reasons presented above in relation to the Schreiber international application, Applicants assert that the nature of the invention that is described in the present application is considerably different from

the subject matter that is disclosed in the Adams patent.

Additional evidence of the differences between the Adams patent and the invention that is described in the present application may be found in the fact that the Adams patent discloses the use of novel boronic ester and acid compounds to *prevent* the degradation of p53 and cyclins. (See the Summary of the Invention.) In contrast to this, it should be noted that the prevention of p53 and cyclin degradation does not play an essential role in the invention that is recited in the present application.

For all of these reasons, Applicants submit that the Adams patent, when combined with the other references cited, does not render the subject matter of the present application obvious.

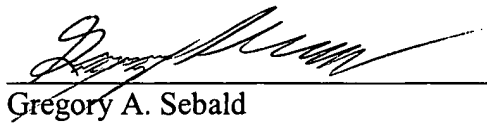
In consideration of all the above, it may be seen that the present invention represents a novel application of proteasome inhibitors, which was not taught or suggested previously and could not be derived from the prior art.

Applicants assert that the application is in condition for allowance. Favorable reconsideration of the present application is therefore requested. If the Examiner feels that a telephone interview may be helpful in this matter, please contact Applicants' representative at 612.336.4728.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
612/332-5300

Date: 12/29/03



Gregory A. Sebald
Reg. No. 33,280
GAS/krn